Research Report

Familial Clustering of Stroke According to Proband Age at Onset of Presenting Ischemic Stroke

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Background and Purpose—The magnitude of inherited risk of stroke may lessen with age, and this would have implications for optimizing genomic approaches to identifying genetic risk factors for stroke. We investigated the relationship between age and inherited risk of stroke.

Methods—Family histories of stroke were obtained in systematic interviews with 310 adult men and women with recent CT- or MR-confirmed ischemic stroke. Probability of stroke in first-degree relatives was analyzed by logistic regression, adjusting for sibship size.

Results—The probability of having a sibling with stroke increased as proband age at stroke presentation increased. Per decade increase in proband age, the odds ratio was 1.65 (95% confidence interval [CI], 1.20 to 2.28; \( P = 0.002 \)) for a concordant sibling and 1.69 (95% CI, 1.15 to 2.49; \( P = 0.008 \)) for \( \geq 2 \) first-degree relatives with a history of stroke.

Conclusions—Clustering of stroke was not greater in families with probands manifesting symptoms of stroke in earlier than later adulthood. The relationship between proband age and positive family history of stroke does not suggest an upper age-limit cutoff for genomewide linkage studies. (Stroke. 2003;34:e89-e91.)

Key Words: age of onset ■ genetics ■ history ■ stroke, ischemic

Family history studies support an inherited component to stroke risk.1–5 Longitudinal survey data from a twin registry of US veterans6 suggest that the magnitude of the inherited component of stroke risk may attenuate with age. When members of the registry were surveyed in 1984 and 1985, the monozygotic concordance rate was 17.7% compared with 3.6% for dizygotic twins, and the relative risk of stroke was estimated to be 4.3. However, in 1997 and 1998, the monozygotic concordance rate was 17% compared with the dizygotic rate of 18.4%.7 Furthermore, in a recent family history study,8 although family history of stroke before the age of 65 years was an independent risk factor for ischemic stroke at any age, it was a stronger risk factor at age 65 years or younger (odds ratio, 1.47 versus 2.25). We explored the relationship between familial clustering of stroke and age at onset in probands presenting with ischemic stroke.

Subjects and Methods

Probands were participants in the Mayo Stroke Family History Study, a prospective registry of adult men and women with recent ischemic stroke. The initial purpose was to establish the feasibility of an affected sibling pair study of ischemic stroke.5 Patients were recruited from the neurology inpatient and outpatient services at Mayo Clinic in Rochester, Minnesota, and Jacksonville, Florida.

Patients were eligible for enrollment as probands if they were 18 years of age or older and presented with ischemic stroke within 180 days after onset of symptoms. The study was approved by the Mayo Foundation Institutional Review Board, and informed consent was obtained from each proband.

Stroke was defined according to World Health Organization criteria9 and classified as ischemic stroke only if computed tomography or MRI of the head done within 7 days after onset of symptoms either identified the symptomatic cerebral infarct or failed to show an alternative cause of the symptoms. Proband age refers to age at onset of the proband’s presenting ischemic stroke. Onset was defined as the time the proband was last known to be at prestroke (baseline) neurologic status.

Patients were not enrolled if they had iatrogenic stroke, stroke due to vasospasm, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Fabry disease, homocystinuria, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, sickle cell anemia, a mechanical mitral or aortic valve, or biopsy-proven central nervous system vasculitis.

Probands’ personal and family medical histories were obtained by reviewing medical records and systematically interviewing probands and/or surrogates. Probands were given an opportunity to contact relatives or review personal records to verify the family history. Parental histories were recorded only for biological parents; sibling histories were recorded only for full siblings. A first-degree relative was considered concordant if the results of the interview indicated a history of stroke. We did not distinguish intracerebral hemorrhage from cerebral infarction in first-degree relatives because of the difficulty of reliably differentiating the 2 conditions by history alone.

Logistic regression models were obtained for each of the following dependent variables: living concordant sibling, any concordant sibling, concordant parent, and any concordant parent or sibling. The explanatory variables were age of the proband and number of siblings, including both linear and quadratic terms. Quadratic terms
were retained in the model only if they were significant at the 0.05 level. To visualize the associations, graphs showing the estimated probability of concordance as a function of age and number of siblings were prepared by using generalized additive models. A test for a heterogeneous association between concordance and age was carried out with the generalized rank-sum test.11 Because of the small number of subjects below 50 years of age, models were fit separately for all probands and for probands 50 years of age or older.

Results

A total of 310 probands (median age, 75 years; mean ± SD, 72 ± 12.1; range, 26 to 97 years; 48% women) were enrolled between January 1999 and August 2000; 188 (61%) were enrolled in Rochester and 122 (39%) in Jacksonville. Of the total, 251 (81%) of probands were incident cases of ischemic stroke. Proband age distribution at stroke presentation was nearly gaussian; 292 probands (94.2%) were older than age 50 years. Median time from stroke onset to enrollment was 5 days.

The probability of having a concordant sibling increased monotonically with sibship size (Fig. 1A). The probability of having a concordant parent was not affected by sibship size (Fig. 1B). Because of the relationship between the probability of having a concordant sibling and sibship size, all other analyses were adjusted for number of siblings per pedigree. Only probands who had at least 1 sibling were included in the subsequent analyses (n=283).

Regression analyses (Table) showed that increases in proband age significantly increased the probability of having a concordant sibling but not the probability of having a living concordant sibling or the probability of having a concordant parent. Increases in proband age also significantly increased the probability of having at least 2 first-degree relatives, either siblings or parents, with a history of stroke.

When the models were fit with only probands 50 years of age or older, results were virtually identical except in the model for risk of having a concordant sibling or parent, in which the odds ratio for age by decade was 1.11 (95% confidence interval [CI], 0.86 to 1.43; \( P = 0.445 \)). Figure 2 illustrates the relationship between proband age and probability of a concordant sibling for probands with stroke onset at age 50 years or older.

Attempts at modeling the relationship using a quadratic function or a 2-stage linear function did not explain the probability of having an affected sibling any better than the simple linear model. We also examined the possibility that clustering of stroke in siblings occurs at younger ages (reflecting a genetic etiology) as well as at older ages (reflecting an age-driven etiology). The generalized rank-sum test for a heterogeneous association between concordance of stroke among siblings and proband age was not significant.

Discussion

In this family history study of adult men and women presenting with a recent ischemic stroke, we found that the probability of stroke clustering within a sibship showed a roughly monotonic rise with proband age at stroke onset. The same pattern of clustering within sibships may not apply to children or young adults. A general tendency for sibling stroke rates to rise with proband age is expected because siblings and probands age concurrently. However, our purpose was to investigate whether the age effect might be overwhelmed by a genetic predisposition to stroke that might play a greater role in younger than in older patients. We did not find greater clustering of stroke within younger sibships.
Figure 2. Probability of having a concordant sibling in relation to proband age at onset of stroke (after adjusting for sibship size) in the subset of patients age 50 years or older with at least 1 sibling. Dotted lines show 95% confidence bands. A, An analysis restricted to probands with first-ever and recurrent ischemic stroke. B, An analysis restricted to probands with first-ever ischemic stroke.

This implies that the magnitude of inherited stroke risk does not attenuate rapidly from age 50 to 80 years. Our study did not identify a clear upper age limit for adults with so-called sporadic or common stroke to be included in a genomic study searching for ischemic stroke risk factors. The study does not provide insight into planning genomic studies of stroke in children or young adults. Twin studies and other family history studies showing that family history is a greater risk factor in stroke affecting younger rather than older adults imply that fewer pedigrees would be required to perform genomic studies in a younger (≤65 years) rather than an older stroke population. However, genome scanning should be performed in both younger and older stroke populations because of the genetic heterogeneity of stroke.

Different genes may be involved at different age levels.

Although self-reporting of a medical diagnosis of stroke has high sensitivity and specificity, the reliability and validity of obtaining stroke status of first-degree relatives through proband and surrogate report are not well known. Given that we did not independently validate proband-reported stroke histories in first-degree relatives, it was reassuring to find that the probability of having a stroke-affected sibling increased linearly as a function of sibship size. This finding serves as a positive control for the validity of proband-reported sibling stroke histories. Absence of a relationship between parental history of stroke and sibship size serves as a negative control.

We conclude that it would be inappropriate at present to target only younger adults in genomic studies that assess possible ischemic stroke risk factor loci or polymorphisms. The ongoing Siblings With Ischemic Stroke Study does not specify an upper age limit for proband eligibility. Investigators from the deCODE Genetics group have successfully identified a stroke susceptibility locus on 5q12 at D5S2080 (designated STRK1; LOD score, 4.86 for ischemic stroke and TIA) without limiting their genomewide search to any one particular age group. Once risk factor genes are identified, it would be of interest to assess relative risk for stroke as a function of age.

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